UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/927,824	08/10/2001	William Gavin	10275-146001 / TCI-146	6238

31904 7590 11/18/2002

GTC BIOTHERAPEUTICS, INC.
175 CROSSING BOULEVARD, SUITE 410
FRAMINGHAM, MA 01702

EXAMINER	
AFREMOVA, VERA	
ART UNIT	**PAPER NUMBER**
1651	7

DATE MAILED: 11/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/927,824	Gavin et al.
Examiner	**Art Unit**
Vera Afremova	1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 10, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-26* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *4, 5*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-26 are pending and under examination.

Claim Rejections - 35 USC § 112

Claims 3, 7, 11, 14, 15, 17, 20, 23 and 24-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 recites the limitation "the cryoprotectant buffer". There is insufficient antecedent basis for this limitation in the method of claim 1.

Claim 7 is indefinite because it is unclear what is encompassed by "maintained at first temperature" for 4-21 hours. Is it a total time period required for the "cooling" step? Is it a total time period required for the adding step ? Is this step intended between steps of adding and of freezing? There is insufficient antecedent basis for this limitation in the method of claim 1.

Claim 11 is indefinite because it is unclear what is encompassed by "maintained at the second temperature" for 7-20 minutes. Is it a total time period required for the "freezing" step? Is it a time period "sufficient" to equilibrate glycerol and sperm after the freezing to the second temperature but before storing at a third temperature (see claims 1 and 12) ? When does it occur? There is insufficient antecedent basis for this limitation in the method of claim 1.

Claims 14, 15, 20 and 21 are indefinite and confusing with regard to the glycerol addition. Claims 14 and 15 appear to exclude each other limitations drawn to either presence or absence of glycerol in the same cryoprotectant buffer in the method of claim 13 which

encompasses the use of only one "first cryoprotectant buffer". Are two different methods intended? Are two different "first" cryoprotectant buffers intended, for example: one for cooling and the other for after the cooling but before freezing? It is unclear whether or not the "first" buffer of claim 14 is actually the "second" buffer of claims 20 and 21 since they all have the same glycerol concentrations. Does claim 14 contain a typing error?

Claim 17 is indefinite because it is unclear what is encompassed by "maintained at first temperature" for 4-21 hours. When does it occur? There is insufficient antecedent basis for this limitation in the method of claim 13. Further, both claims 17 and 19 are indefinite, confusing and redundant because they require overlapping ranges such as 4 hours, for example.

Claim 20 is rendered indefinite by the phrase "further cooled to the second temperature" because it is uncertain whether or not this phrase encompasses the c) step of "freezing" at a "second" temperature or whether this phrase is drawn to incorporation of additional step.

Claim 23 is indefinite because it is unclear what is encompassed by "maintained at the second temperature" for 7-20 minutes. Is it a total time period required for "freezing" step? Is it a time period required for after the "freezing" but before "storing"? There is insufficient antecedent basis for this limitation in the method of claim 13.

Claim 24 is rendered indefinite by repetitions of the phrase "said" sperm, for example: see steps c), d) and I). Regardless the fact that the method appears to comprises consecutive steps by virtue of using an alphabetical order of steps, it is not particularly clear whether or not each consecutive phrase "said" refers to the immediate prior step because there are several variously

treated sperm samples in the method of claim 24. It is suggested to particularly point out antecedent basis of all sperm samples.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4-6, 8-16, 18-22 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by SU 986411 [IDS-AL].

Claims are directed a method of preserving mammalian sperm wherein the method comprises step of combining sperm with a first cryoprotectant buffer, step of cooling the sperm to a first temperature between from about 0°C to 2°C to about 10°C , step of adding a second cryoprotectant, step of freezing sperm to a second temperature from about -40°C to about -100°C or from about -60°C to about -90°C. Some claims are further drawn to the use of 5-10% glycerol in the second cryoprotectant buffer. Some claims are further drawn to the use of the cooling rate of about 0.2°C to 0.5°C per minute over the corse of about 1.5-4 hours. Some claims are further drawn to the use of the second cooling stage to the second temperature of about -40°C to about -100°C or of about -80°C. Some claims are further drawn to maintaining

or holding the cooled sperm at the second temperature for 7-20 minutes. Some claims are further drawn to a method of making an animal by fertilizing an oocyte with the preserved sperm.

SU 986411 discloses a method of preserving mammalian or bovine sperm wherein the method comprises step of combining the sperm with a first typical cryoprotectant buffer containing egg yolk (col. 3, line 18), step of cooling the sperm to a first temperature of about 4°C using a slow cooling rate of about 0.2°C to 0.5°C per minute over the corse of about 1-3 hours (table 1), step of adding a second cryoprotectant buffer comprising 10% glycerol (col. 3, line 45), step of maintaining the cooled sperm with the glycerol containing cryoprotectant buffer for 30 minutes at about 4°C to 5°C (English abstract, col. 3, last line and col. 4, line 7), step of freezing sperm in vapors of liquid nitrogen by maintaining or holding at second temperature of about -120° C to about -160°C for 8-8.5 minutes (col. 3, lines 8-10 and col. 4, lines 13-16) and step of storing the sperm in liquid nitrogen or at the third temperature (col. 4, line 25). Further, the cited patent SU 986411 discloses steps of thawing the frozen sperm and using the stored sperm for oocyte fertilization (col. 4, line 47), thereby making an animal within the meaning of the presently claimed invention (claim 26).

With respect to the claims 1, 2, 4-6, 8, 9, 12 and 26 the method for preserving mammalian sperm of the cited patent SU 986411 is considered to be identical to the applicants' method for preserving mammalian sperm because they both comprises identical active steps and identical structural elements.

With respect to claim 11, which is considered to further limit the step of freezing or the step of freezing by maintaining and which indicates particular time but not particular "freezing" temperature, the method of cited patent is considered to be identical to the claimed method because the SU 986411 teaches step of freezing by maintaining the sperm at "freezing" temperature for about 8-8.5 minutes (English abstract or col. 3, lines 9-10 or col. 4, lines 12-16) what is within the claimed ranges of 7-20 minutes intended for freezing/maintaining step.

With respect to claims 10 and 13, the cited method is considered to be identical to the claimed method since the methods of claims 10 and 13 are not limited to any time period required for "freezing" or for exposing the sperm sample to the second temperature. Thus, the freezing of the sperm sample down to the level of temperature of the liquid nitrogen vapors of about -120°C to about -140°C as disclosed by the cited SU will necessarily utilize the temperatures which are above the liquid nitrogen temperatures including from -40°C to about -100°C or from -60°C to about -90°C as required by the present claims 10 and 13 for at least some period of time. Therefore, claims 15, 16 and 18-22, which are dependent on claim 13, are also anticipated by the cited patent SU 986411, because these claims are drawn to the use of the same steps and structural elements in the same method for preserving mammalian sperm as disclosed by SU 986411.

With respect to claim 14, which is drawn to the use of a "first" cryoprotectant buffer comprising glycerol at temperature between 2°C to 10°C, the claimed invention is anticipated by

SU 986411 which teaches addition of the glycerol containing buffer at temperature between 4°C to 5°C (see English abstract or col. 3, last line) what is within the scope of the claimed method.

With respect to the claims 15, 20 and 21, which are drawn to the lack of glycerol in "first" cryoprotectant but incorporation of glycerol in "second" cryoprotectant, the claimed invention is anticipated by SU 986411 which teaches the initial sperm cooling with a typical cryoprotectant without glycerol and the addition of glycerol to the sperm sample before freezing (see English abstract or col. 3, last line) what is within the scope of the claimed method.

Therefore, the cited SU 986411 anticipates the presently claimed invention.

Claims 13, 15-19 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by US 3,940,943 [IDS-AA].

Claims are directed a method of preserving sperm wherein the method comprises step of combining sperm with a cryoprotectant buffer, cooling the sperm to a first temperature between about 2°C to about 10°C, freezing sperm to second temperature of about -60°C to about -90°C and storing the sperm in liquid nitrogen. Some claims are further drawn to the absence of glycerol in the first cryoprotectant buffer. Some claims are further drawn to the use of the cooling rate of about 0.2° C to 0.5 °C per minute. Some claims are further drawn to cooling or maintaining the sperm sample at the first temperature between about 2°C to about 10° C for a period of time 1.5-4 hours or 4-21 hours. Some claims are further drawn to a method of making an animal by fertilizing an oocyte with the preserved sperm

US 3,940,943 discloses a method of preserving sperm encompassing the use of multistage cooling and/or freezing the sperm (col. 2, lines 33-35) wherein the method does not require the use of glycerol (col. 2, line 41). The disclosed method comprises step of combining sperm with a typical cryoprotectant buffer containing 25% egg yolk (col. 3, line 1), step of cooling the sperm with a slow cooling rate less than 1°C per minute to the temperature of about 3°C to about 8°C (col. 3, lines 20-22), step of holding the cooled sperm sample from 30 minutes to several hours (col. 3, line 24), step of rapid freezing the sperm to a second temperature of about -4° C to about -100°C (col. 3, lines 49-50) and step of storing the sperm in liquid nitrogen (col. 3, line 64). The cited patent US 3,940,943 further discloses thawing the frozen sperm (col. 4, lines 1-5) and using the preserved sperm for oocyte fertilization (col. 5, line 39), thereby making an animal within the meaning of the presently claimed invention (claim 26). Thus, the cited patent is considered to anticipate the claimed invention because it teaches the identical method of mammalian sperm preservation encompassing the use of slow cooling and rapid freezing rates in the absence glycerol or in the absence glycerol in a "first" cryoprotectant buffer as encompassed by the claimed invention of claims 13, 15, 16, 18 and 22. The cited method is considered to be identical to the method of claim 17 and 19 because the cited method comprises step of cooling or holding the sperm at "first" temperature of about 3°C to 8°C for about 30 minutes to several hours including 4 hours, for example, as required by both claims 17 and 19.

Therefore, the cited US 3,940,943 anticipates the presently claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over SU 986411 [IDS-AL] and US 3,940,943 [IDS-AA] taken with Royere et al.[IDS-AQ].

Claims 1, 2, 4-6, 8-10, 11-16 and 18-22 as explained above are directed a method of preserving mammalian sperm and storing the sperm wherein the method encompasses step of slow cooling to a first temperature of about 2°C to about 10° C, step of rapid freezing at second temperature of about -60°C to about -90° C of the sperm and the use of cryoprotectant buffers without glycerol for cooling the sperm and with 5-10% glycerol for treating the sperm before freezing. Claim 3 is further drawn to the use of cryoprotectant buffer comprising egg yolk at concentration of 10-30 %. Some claims are/are further drawn to maintaining the cooled sample for 4-21 hours before freezing at the first temperature (claims 7, 17 and 24). Some claims are/are further drawn to freezing the cooled sample by maintaining the cooled sample at the second temperature for 7-20 minutes or 10-15 minutes (claims 11, 23 and 24). Some claims are further drawn to thawing of frozen sperm and fertilizing oocyte, thereby practicing a method of making an animal (claims 25 and 26).

Both cited patents SU 986411 and US 3,940,943 are relied upon as explained above for the disclosure of methods for preservation of mammalian sperm by protocols encompassing slow cooling and rapid freezing of the sperm diluted in cryoprotectant buffers wherein the cooling/freezing rates as disclosed by the cited patents are within the ranges which are presently claimed. Both cited patents SU 986411 and US 3,940,943 disclose thawing of frozen sperm and fertilizing oocyte with the stored sperm, thereby practicing methods of making animals within the scope of the presently claimed invention. In addition, the reference by Royere et al. confirms the beneficial effects of using controlled slow cooling and rapid freezing stages (page 557, col.1, lines 1-4) and further thawing at 37°C (page 557, col. 1) in the methods for mammalian sperm preservation and further fertilization which are taught by both cited patents SU 986411 and US 3,940,943.

With respect to the cryoprotectant compositions in the method for sperm preservation, the cited SU 986411 clearly teaches the use of glycerol by adding glycerol before freezing to the cooled sperm diluted in a conventional cryoprotectant buffer comprising egg yolks. But it is silent with regard to egg yolk concentration in a typical or conventional formulation. However, US 3,940,943 indicates that a typical formulation of a cryoprotectant buffer comprises egg yolk at a concentration of 25 % in the method for mammalian sperm preservation (col. 3, line 1). Although the cited US 3,940,943 discloses a particular method which does not require glycerol utilization, it suggests the use non-toxic concentrations of glycerol (col. 2, lines 44-45). And the cited patent SU 986411 clearly teaches the use of a non-toxic 10% glycerol which is added to the

cooled sperm in the method for sperm preservation and fertilization. In addition, the cited reference by Royere et al. teaches that the optimal concentration of glycerol is about 7.5% for preserving mammalian sperm (page 556, col.1, lines 1-3) and it also teaches the concept of reducing possible toxic effects of glycerol by adding glycerol to the cooled sperm sample before freezing (page 556, col. 2, lines 8-10).

With respect to the limitations of claims 7, 17 and 24, the cited SU 986411 teaches the steps of cooling including maintaining the sperm sample at temperature of 4°C to 5°C for 30 minutes but it is lacking particular disclosure with regard to a longer period of holding for several hours including 4-21 hours before freezing. However, the cited US 3,940,943 teaches that at the stage of cooling/maintaining at first temperature the cooled sperm samples might be held from 30 minutes to several hours including 4-21 hours in order to optimize the cooling and/or packaging procedures in the method for sperm preservation (col. 3, lines 22-26).

With respect to the limitations of claims 11, 23 and 24, the cited SU 986411 teaches the step of rapid freezing by maintaining the sperm sample mixed with non-toxic concentration of glycerol at temperature of about -120°C to -140 °C for a short period of 8-8.5 minutes before storing the frozen sperm in liquid nitrogen. But it is lacking a particular disclosure with regard to freezing by maintaining the sperm at -60°C to -90 °C for 7-20 minutes or 10-15 minutes. However, the cited US 3,940,943 teaches the rapid freezing of sperm by maintaining the sperm at the lower temperature that in the method of SU 986411 such as between -4°C to -100 °C , what is within the presently claimed range. The time of exposure to the temperature between -

4°C to -100 °C in the method of US 3,940,943 is about 3-10 minutes since the freezing rates are from 10°C/min to 30°C/min as disclosed in US 3,940,943 (col. 3, lines 49-56) what is within the presently claimed range. Thus, the cited US 3,940,943 teaches a decrease in freezing temperatures for the freezing/maintaining step in the method for mammalian sperm preservation. The cited US 3,940,943 also teaches that the optimum for the rapid freezing step might be modified depending on packaging type and sample volume (col. 3, lines 52-53). The cited US 3,940,943 also teaches that the sperm samples should be maintained for a sufficient time to allow the stabilization of membrane permeability and osmotic pressure alterations at the initial freezing temperatures (col. 3, lines 39-42).

Therefore, it would have been obvious at the time the claimed invention was made to practice a mammalian sperm preservation method encompassing the use of slow cooling/rapid freezing of sperm and the addition of glycerol to the cooled sperm before freezing with a reasonably expectation in success for preserving the sperm intended for fertilization because substantially similar protocols have been taught and suggested in the prior art as adequately demonstrated by all cited references {SU 986411; US 3,940,943; Royere et al.]. One of skill in the art would have been motivated to use typical cryoprotectant buffer formulations with egg yolks and glycerol for the expected benefits of sperm preservation intended for fertilization as demonstrated in the prior art {SU 986411; US 3,940,943; Royere et al.]. One of skill in the art would have been motivated to add glycerol to the cooled sperm sample before freezing for the expected benefits in reducing possible toxic effects of glycerol on mammalian sperm {SU

986411; Royere et al.}. One of skill in the art would have been motivated to increase or to modify the time for holding sperm samples at first cooling temperature and/or at second freezing temperature in order to optimize cooling/freezing and packaging procedures as suggested by the prior art {US 3,940,943}. One of skill in the art would have been motivated to maintain the sperm samples at the initial or at the low freezing temperature in order to stabilize membrane permeability and osmotic pressure alterations induced by freezing as suggested by the prior art {US 3,940,943}. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Although the claim 24 is directed to a particular sequence of steps, the prior art teaches the similar sequence of steps including substantially similar, if not identical, limitations with regard to cryoprotectant buffer components, temperatures and time of exposure to cooling/freezing temperatures. Thus, the claim 24 is not considered to encompass any particular differences which would distinguish the claimed sequence of steps from the prior art sequences of steps in the methods for sperm preservation comprising slow cooling/rapid freezing of the sperm and the use of cryoprotectant buffer with non-toxic glycerol concentrations after sperm cooling but before sperm freezing as demonstrated by the cited references combined.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351. The examiner can normally be reached on Monday to Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vera Afremova

Art Unit 1651

November 14, 2002.

V. Afremova

VERA AFREMOVA

PATENT EXAMINER